

Mental Neuropathy as Initial Manifestation of Metastatic Breast Cancer: A Case Report and Review of the Literature

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Abstract

Introduction: Mental neuropathy is a sensory neuropathy characterized by hypoesthesia or paresthesia of the chin and lower lip. It can be a symptom of a latent malignant disease.

Case Presentation: This report presents a case of a 34-year-old woman with a history of breast cancer who complained of severe pain and numbness of the right lower lip. We reviewed numerous reliable articles (through PubMed and Google Search) in relation to mental neuropathy and its possible causes.

Conclusion: Given that the reports of mental neuropathy have often been associated with malignancies, patients that complain of sensory impairment and numbness of the mental region should be examined carefully.

Key Words: Breast Neoplasms, Neoplasm Metastasis, Neuropathy, Paresthesia

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Introduction

Mental neuropathy (numb chin syndrome) is a sensory neuropathy characterized by change in sensation and numbness of the chin and lower lip. This is a consequence of loss in sensory function of the mandibular branch of the trigeminal nerve, which may be associated with a sense of lip thickening. This neuropathy is unilateral in most cases, but bilateral involvement may also occur simultaneously or over time [1-4].

Several factors and conditions may be associated with mental neuropathy, including injections or other dental procedures (iatrogenic), dental infections, osteomyelitis of the mandible, jaw cysts, traumatic injuries, idiopathic trigeminal

neuropathy, and atrophy of the mandible. Mandibular atrophy is a major cause of this neuropathy in the elderly, and is in fact a natural part of the aging process. Radiotherapy and exposure to chemical agents such as trichlorethylene and allopurinol, also play a role in the development of mental neuropathy. Additionally, there have been reports of a relationship between this neuropathy and sickle cell anemia, multiple sclerosis, amyloidosis, diabetes, viral infections, vasculitis after vaccination, Lyme disease and temporal arteritis (as the first symptom of the disease). For example, in case of multiple sclerosis (a demyelinating disease), it is obvious that it can cause neuropathy

in various parts of the body including the maxillofacial region. [1-9].

While mental neuropathy can be associated with some benign conditions and diseases, it should not be considered a typical and banal symptom. In other words, mental neuropathy is a very important sign and it should not be considered a typical and chronic symptom. This neuropathy can be a symptom of a latent malignant disease, because it is associated with malignant tumors or diffuse metastatic diseases in many cases. The most common malignancies associated with mental neuropathy include hematologic malignancies and cancers of the breast, lungs, thyroid, prostate, and colon [3,4,7,9,10].

Charles Bell, in the early 1800s, described mental neuropathy in an elderly woman with breast cancer, and this was probably the first report of malignancy associated with mental neuropathy. He researcher also stated that other factors such as jaw tumors, trauma and drug toxicity are common causes of neuropathy [11]. Since then, numerous reports have been published about the relationship of different types of cancer and mental neuropathy, with lymphoma and breast cancer being the most prominent [12-16].

In this paper, we report a case of a 34-year-old woman with mental neuropathy and a history of breast cancer, and review articles on patients with mental neuropathy. We observed that, in contrast to most of these articles, the patient's mandibular X-ray showed no bone change suggestive of mental nerve involvement or pressure on the nerve, possibly indicating a rarity in our patient.

Case Presentation

A 34-year-old non-smoker female complaining of severe pain and numbness of the right lower lip was referred for treatment to the Oral and Maxillofacial Diseases Department of Tehran University Dental School by her oncologist. She mentioned a history of cancer (invasive ductal carcinoma) in her right breast three 3 years previously, which had gone into remission after eight sessions of chemotherapy. Since that time, she performed routine blood tests, mammography, ultrasound and bone scan every six months, and each time the results were normal. It should be noted that there was no history of any surgery in

the region of trigeminal nerve including its mandibular branch (V3).

We performed a complete clinical examination of the teeth, periodontal tissue, salivary glands and oral mucosa. On clinical examination, the teeth were healthy and vital. Periodontal status was also normal (no bleeding on probing and no pocket with more than 3 mm depth). Oral mucosa including the cheeks, floor of the mouth, hard and soft palate and tongue (ventral, dorsal and lateral surfaces) were normal, and showed normal response to examination by dental explorer. The patient's lip had normal appearance, but the right and left sides of her lower lip had not the same feeling on examination by dental explorer; the right side did not show a reaction, the left side was normal. Except for the right lower lip sensory impairment, there was no particular problem on neurological examination. A panoramic radiograph was ordered, and examination showed that the previous dental fillings did not show any recurrent caries, and the teeth without fillings were still caries-free. No lesion was observed in the periapical area, alveolar bone, maxilla and mandible.

The results of clinical and paraclinical examination showed that paresthesia in the patient could not have a dental origin, and therefore there was a possibility that it was related to metastasis of her underlying disease. The patient was therefore referred back to her oncologist for evaluation. He eventually ordered blood tests and head and neck MRI to detect possible metastasis.

The results showed white and red blood cell counts and some indices of red blood cells (including MCH and MCHC) were lower than the normal range. The result of MRI without IV contrast of the brain was normal, but the cervical spine was abnormal and was reported as follows:

- Post op changes at the C2-3 level.
- Abnormal signal intensity area was seen in the posterior part of C5 body.
- There were abnormal signal intensity areas in upper dorsal spine, too.
- Findings were indicative of metastasis.
- Mild scoliosis.
- Loss of cervical lordosis.

With a diagnosis of metastasis, radiation therapy was placed on the agenda. Almost six months after the appearance of neuropathy and initiation of

treatment, the patient stated significant weight loss (20 kg) and severe disability.

Discussion

Mental neuropathy (numb chin syndrome) is caused by damage to the inferior alveolar nerve, responsible for innervation of the chin and lower lip. This nerve is a branch of the trigeminal nerve and is mostly sensory; thus, patients with neuropathy of this nerve experience change of sensation in the affected area [1-4,17,18].

Several conditions and diseases, including benign and malignant, can be the cause of this neuropathy. For example, jaw trauma and infections, mandibular atrophy, metastatic spread around the nerve, tumor compressing the nerve, or use of certain chemotherapy drugs (as a side effect) can be cited [4,19]. The literature covers a wide range of etiologic factors as a cause of mental neuropathy, but in the context of this patient, our interest was neuropathy caused by primary and metastatic tumors and investigation of cases reported with this condition (Table 1). The first reported case was in 1830 by Charles Bell in a patient with breast cancer who suffered from numbness on one side of the lower lip. Examination revealed a hard glandular mass in the jaw, which was most probably applying pressure on the inferior alveolar nerve, resulting in numbness of that area [11]. Later studies reported a positive relationship between mental nerve neuropathy and metastatic cancer. A study on 42 patients showed that the most common malignancies associated with this neuropathy were breast cancer and lymphoproliferative neoplasms [13].

In addition to metastatic cancers, primary tumors can also cause mental neuropathy. For example, researchers have reported that this neuropathy can result from primary osteosarcoma of the mandible, or direct invasion of squamous cell carcinoma of the lip [20].

Pathogenic mechanisms that cause mental neuropathy in patients with metastatic cancers are often unknown. Presumptive mechanisms include direct pressure on the inferior alveolar nerve due to metastasis to the jaw, neoplastic infiltration around the nerve, blood or lymphatic spread to the central

nervous system, intracranial involvement of the mandibular nerve by lesions, metastasis to the skull base, and also leptomeningeal seeding [2,12,13,16,21-23]. Additionally, based on the results of some empirical studies, the effect of tumor necrosis factor on the nerves could be the possible cause of paresthesia; so it is thought that the production of substances such as tumor necrosis factor in the location of the tumor causes hypoparesthesia. In fact, this neuropathy could represent a non-metastatic neurologic manifestation of the malignancy [4,7,24,25].

Mental neuropathy, osteolytic lesion of the jaw, progressive increase in the size of the mental foramen, or enlarged mandibular canal secondary to thickening of the nerve can be caused by the primary tumor or metastasis [2,20,26]. In case of mental neuropathy associated with malignancy, the results of bone scan and mandibular x-rays may be normal; nevertheless, progressive or recurrent skeletal disease exists, and can be discovered by radiographic examination of other areas (which can be considered as the source of neuropathy) [2]. In this study, the panoramic radiograph of the patient was normal. In MRI examination of the head and neck, some changes were seen in the cervical spine (C2-3) as evidence of metastasis from her previous tumor. Several studies have noted the occurrence of metastasis in the spine and spinal cord in patients with malignancies associated with malignancy-related mental neuropathy [2,5,9,27]. In previous studies on patients with mental neuropathy, mandibular imaging often showed a bony lesion at the time of admission of most cases (unlike our case) [4,5,28], and also in some cases, the lesion was detected later [29]. Imaging of the head and neck in our patient did not show any lesion in the mandibular region, but presence of lesion in the cervical spine can validate mental neuropathy as a referral symptom from the neck area. This could be unique to our patient, or there may be a previous case, which was not mentioned as a cause of mental neuropathy. Of course, in addition to spinal cord lesion, the patient might have trigeminal nerve involvement, and MRI is not well capable of detecting it and requires more advanced imaging techniques such as positron emission tomography scan.

Table 1. Reports of mental neuropathy in patients with/ history of different types of cancer

Author	Year	Age (year)	Sex	Type of malignancy	Primary/ Metastatic	Lesion in jaw
Sudha ⁽⁴¹⁾	2015	56	F	Breast carcinoma	Metastatic	+
García-Lamazares ⁽²⁷⁾	2014	62	F	Breast cancer	Metastatic	-
Chapa ⁽²⁹⁾	2014	39	F	Breast sarcoma	Metastatic	Delayed + 5 months
Barman ⁽⁹⁾	2014	52	F	Breast carcinoma	Metastatic	? *
Kota ⁽¹⁸⁾	2013	48	F	Breast cancer	Metastatic	? *
Oravivattanakul ⁽⁴²⁾	2013	51	F	Breast cancer	Metastatic	? *
Zaheer ⁽¹⁾	2013	62	F	Lung adenocarcinoma	Metastatic	-
Orhan ⁽⁵⁾	2011	69	F	Breast carcinoma	Metastatic	+
Divya ⁽³⁾	2010	66	F	Renal cell carcinoma	Metastatic	-
Narendra ⁽²⁸⁾	2009	40	M	SCC of Esophagus	Metastatic	+
Colella ⁽⁴⁾	2008	44	M	Myeloma	Primary	+
Colella ⁽⁴⁾	2008	28	F	Burkitt's lymphoma	Primary	+
Colella ⁽⁴⁾	2008	39	M	Osteosarcoma	Primary	+
Colella ⁽⁴⁾	2008	68	F	Breast carcinoma	Metastatic	+
Colella ⁽⁴⁾	2008	65	F	Intraosseous adenocarcinoma	Primary	+
Colella ⁽⁴⁾	2008	39	M	Intraosseous carcinoma	Primary	+
Colella ⁽⁴⁾	2008	47	F	Intraosseous carcinoma	Primary	+
Colella ⁽⁴⁾	2008	46	F	Thyroid carcinoma	Metastatic	+
Colella ⁽⁴⁾	2008	59	M	Lung cancer	Metastatic	+
Colella ⁽⁴⁾	2008	80	M	Lung cancer	Metastatic	+
Colella ⁽⁴⁾	2008	62	F	Breast carcinoma	Metastatic	+
Colella ⁽⁴⁾	2008	53	F	Breast carcinoma	Metastatic	+
Smith ⁽⁷⁾	2008	79	F	Breast carcinoma	Metastatic	-
Montero Pérez ⁽¹⁰⁾	2003	65	M	Small cell lung carcinoma	Metastatic	-
Laurencet ⁽²⁾	2000	56	F	Small cell lung carcinoma	Metastatic	delayed +
Laurencet ⁽²⁾	2000	47	M	Prostate adenocarcinoma	Metastatic	-
Laurencet ⁽²⁾	2000	77	F	Breast cancer	Metastatic	-
Laurencet ⁽²⁾	2000	37	F	Breast carcinoma	Metastatic	-
Laurencet ⁽²⁾	2000	68	M	Prostate adenocarcinoma	Metastatic	-
Halachmi ⁽²²⁾	2000	71	M	Prostate carcinoma	Metastatic	-

* : Data was not available

Mental neuropathy associated with malignancy generally appears at the time of tumor progression or recurrence, with an average delay of four years since the first diagnosis of cancer; although this interval varies by malignancy. For example, this time for patients with breast cancer is four years (three years in our patient). A noteworthy issue is

that mental neuropathy occurs prior to disease recurrence in more than 30% of cases. Another important issue regarding mental neuropathy is that about 47% of cases occur before the diagnosis of malignancy. The interval between the emergence of neuropathy, as the first symptom, and diagnosis of neoplasia has not been generally mentioned but

varies from several weeks to a few months since this symptom is often overlooked by patients and physicians. The emergence of mental neuropathy in malignant conditions is a harbinger of a worse prognosis for the disease, because most patients die within a short period after that [2,13,30].

It should be noted that in some studies, despite a history of malignancy in patients with mental neuropathy, histopathological examination of the bony lesion of the jaw showed a nonmalignant lesion such as bisphosphonate-induced osteonecrosis or osteochemonecrosis with secondary bacterial osteomyelitis, because as mentioned earlier, some drugs used for malignancies including bisphosphonates, taxanes, etc., are able to cause peripheral neuropathy in various ways including development of osteonecrosis and cellular mechanisms. On the other hand, persistent inflammation resulting from infection of the jaw also causes pressure on the inferior alveolar nerve and results in development of neuropathy [3,31,32]. Several cases of this type of neuropathy have been reported in the literature [3,31,33,34].

The emergence of peripheral neuropathy in patients undergoing chemotherapy can be caused due to medications. One of the debilitating side effects of most chemotherapy agents is peripheral neuropathy, which is mainly apparent in patients receiving platinum salts, vinca alkaloids and taxanes. Taxanes (docetaxel and paclitaxel) are the most important drugs used for treatment of breast cancer. Thus, patients with breast cancer receiving this drug class often suffer from neuropathy caused by medication side effects during treatment. However, this side effect can affect the patient for many years and sometimes indefinitely [35-39]. In our reported patient, mental neuropathy cannot be attributed to chemotherapy drugs, because the neuropathy had developed recently, but chemotherapy had finished three years earlier, and the patient also had no signs of sensory impairment during treatment.

A notable issue is that in some reported cases of mental neuropathy in patients with malignancy, the patient did not have neuropathy at first, but complained of other symptoms caused by metastasis. In these patients, mental neuropathy developed during the follow-ups and after a while

following initiation of chemotherapy or during the use of bisphosphonates (for prevention of bone metastasis) [2]. Since these medications can lead to neuropathy, our rationale is that since malignancy is being treated, it seems that mental neuropathy is most likely caused by chemotherapy, the use of bisphosphonates, and also in some cases, a combination of both, rather than metastatic spread of malignancy.

In some studies on mental neuropathy caused by breast cancer, the occurrence of symptoms at the same time or before the emergence of neuropathy has been noted. These include other neurological disorders (such as diplopia), chest pain, anorexia, weight loss, perspiration, arthralgia, vomiting, and dorsalgia, although it seems that some of these symptoms have little to do with the nature of disease [2,5] (Table 2). Moreover, in some reports, the occurrence of mental neuropathy was bilateral [2,40]. In our patient, unlike the aforementioned studies, no sign or symptom was observed before or after development of mental neuropathy, and the neuropathy was also unilateral.

One advantage of the present study is that in contrast to most similar previous studies, the histologic type of breast cancer was determined (invasive ductal carcinoma). Among the reviewed articles, only a few mentioned the histological type of breast cancer [9,41]. Given that the type of breast cancer may be effective on the occurrence of mental neuropathy or its incidence rate, the relationship between the histological type of breast cancer and the emergence of neuropathy should be further examined.

The incidence of mental neuropathy is not measurable through the articles, the main reason being the lack of reporting of many cases, and also because this symptom is typically ignored. Since the reporting of neuropathy has often been associated with malignancies rather than other systemic diseases, patients who present with the apparently minor complaint of sensory impairment and numbness of the mental region should be examined carefully and systematically to determine the underlying cause of this condition.

Conflict of interest

The authors report no conflict of interest.

Table 2. Reports of mental neuropathy in patients with a history of breast cancer

Author	Year	Age (year)	Type of breast cancer	Lesion in jaw	Sign & Symptoms	Follow-up
Sudha ⁽⁴¹⁾	2015	56	Invasive ductal carcinoma	+	-	? *
García-Lamazares ⁽²⁷⁾	2014	62	? *	-	-	Died after 2 months
Chapa ⁽²⁹⁾	2014	39	High-grade sarcoma	Delayed +5 months	Palpable lymph nodes in mandible, tenderness in tooth, gingivitis	Died after 19 months
Barman ⁽⁹⁾	2014	52	Infiltrating duct carcinoma	? *	-	? *
Kota ⁽¹⁸⁾	2013	48	-	+	-	? *
Oravivat-tanakul ⁽⁴²⁾	2013	51	? *	? *	? *	? *
Orhan ⁽⁵⁾	2011	69	? *	+	Chest pain, arthralgia, dorsalgia, perspiration, vomiting, deficiency	-
Colella ⁽⁴⁾	2008	68	? *	+	? *	Survival: 26 months
Colella ⁽⁴⁾	2008	62	? *	+	? *	Survival: 25 months
Colella ⁽⁴⁾	2008	53	? *	+	? *	Survival: 21 months
Smith ⁽⁷⁾	2008	79	? *	-	-	? *
Laurencet ⁽²⁾	2000	77	? *	-	Diplopy	16 months later, was still alive
Laurencet ⁽²⁾	2000	37	? *	-	Spine & ribs pain, anorexia, weight loss, diplopy	Died less than 10 months

* : Data was not available

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